

BIOGRAPHICAL SKETCH

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NAME: Kadosh, David

eRA COMMONS USER NAME (credential, e.g., agency login): kadosh

POSITION TITLE: Associate Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University, Ithaca, NY	B.A.	05/1991	Biological Sciences
Harvard University, Cambridge, MA	Ph.D.	06/1998	Biological Chemistry & Molecular Pharmacol.
University of California, San Francisco, CA	Postdoctoral Fellow	06/2003	Microbiology & Immunology

A. Personal Statement

I am well-qualified to serve as a Sponsor for Xiangya students because I have extensive experience (> 23 years) in yeast molecular biology and genetics research, as well as the background, training and expertise to supervise the proposed studies. As a graduate student at Harvard University my studies focused on transcriptional regulation in the model yeast *Saccharomyces cerevisiae*. I was one of the first to demonstrate that recruitment of histone deacetylases to target promoters causes transcriptional repression; this fundamental mechanism is conserved from yeast to mammals and is known to play a role in a variety of disease processes. As a postdoctoral fellow at the University of California, San Francisco, I shifted my focus to the major human fungal pathogen *Candida albicans* and identified and characterized several key regulators of *C. albicans* filamentous growth and virulence. Using whole-genome DNA microarray analysis I also identified the complete set of genes that is induced in the presence of serum and 37°C (one of the strongest filament-inducing conditions). As an Associate Professor at the University of Texas Health Science Center at San Antonio I am directing a laboratory that has made a number of important contributions towards our understanding of how specific transcriptional regulators control morphology, virulence and biofilm formation in *C. albicans* and other pathogenic *Candida* species. I have successfully administered research projects, hired staff, obtained funding and published manuscripts in high-impact journals. I have also established several highly productive collaborations with members of the large and internationally recognized San Antonio Center for Medical Mycology. In summary, I have extensive experience in conducting successful research projects involving *Candida* species biofilm formation, morphogenesis, virulence, transcriptional regulation, genetics and this experience makes me very well-prepared to supervise the proposed studies. I have also successfully mentored and trained five Ph.D. students, all of whom have obtained independent extramural funding and received F-award fellowships from NIH/NIDCR (two with perfect scores). One former student conducted a postdoctoral fellowship in the Laboratory of Clinical Infectious Diseases at NIH/NIAID and a second carried out a postdoctoral position with a top investigator in the *C. albicans* field at the University of Aberdeen, UK. I plan to use my mentoring and training experience to prepare Xiangya students for a successful career in academic medical research.

B. Positions and Honors**RESEARCH AND PROFESSIONAL EXPERIENCE**

1985, 1986, Research Assistant with Prof. Howard A. Bern, Department of Zoology,

1988 (summers)	University of California, Berkeley
1989-1991	Undergraduate Honors Researcher with Prof. Jeffrey W. Roberts, Department of Biochemistry, Molecular and Cellular Biology, Cornell University
1991-1992	Research Associate, COR Therapeutics, Inc., South San Francisco, CA
1992-1998	Graduate student with Prof. Kevin Struhl, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
1996	Teaching Fellow, Division of Experimental Medicine, Brigham and Women's Hospital, Harvard Medical School
1998-2003	Postdoctoral Fellow with Prof. Alexander D. Johnson, Department of Microbiology and Immunology, University of California, San Francisco (medical leave of absence, 2001-2002)
2003-2005	Postgraduate Researcher with Prof. Alexander D. Johnson, Department of Microbiology and Immunology, University of California, San Francisco
2006-2012	Assistant Professor, Department of Microbiology & Immunology, University of Texas Health Science Center at San Antonio (primary appointment)
2006-2012	Assistant Professor, Department of Medicine, Division of Infectious Diseases, University of Texas Health Science Center at San Antonio
2012-present	Associate Professor, Department of Microbiology & Immunology, University of Texas Health Science Center at San Antonio (primary appointment)
2012-present	Associate Professor, Department of Medicine, Division of Infectious Diseases, University of Texas Health Science Center at San Antonio

HONORS

Golden Key National Honor Society (1989-1991)
 Howard Hughes Medical Institute Undergraduate Research Scholar (1990-1991)
 B.A., with Distinction in All Subjects and *magna cum laude* (1991)
 National Science Foundation Predoctoral Fellow (1992-1995)
 Albert J. Ryan Fellow (1995-1998)
 Damon Runyan Cancer Research Foundation Postdoctoral Fellow (1998-2001)
 Finalist, Burroughs Wellcome Fund Career Award in Biomedical Sciences (2002)
 UCSF NIH Biochemistry Training Grant (2002-2003)
 UTHSCSA Executive Research Committee Fund New Investigator Award (2006-2007)
 Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Diseases Award Institutional nominee (2007, 2008, 2010, 2011)
 Beckman Young Investigator Award Institutional nominee (2008)
 Burroughs Wellcome Fund Junior Faculty Travel Grant (2008)
Proceedings of the National Academy of Sciences USA Recruited Author (2009)
 Voelcker Fund Young Investigator Award (2009)
 Finalist, Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Disease Award (2011)
 San Antonio Life Sciences Institute Innovation Challenge Award (2014)
 Institute for Integration of Medicine and Science-Clinical and Translational Science Award (2014)
 Faculty of the Year, UTHSCSA Department of Microbiology & Immunology (2015)

PROFESSIONAL SOCIETIES: American Society for Microbiology (National and Texas Branch) (2006-present), International Society for Human and Animal Mycology (2014-present), Medical Mycology Society of the Americas (2007-present), San Antonio Center for Medical Mycology (2006-present)

C. Contribution to Science

1. My graduate work focused on basic transcriptional regulatory mechanisms in the model yeast *Saccharomyces cerevisiae*. More specifically, I was one of the first to demonstrate that recruitment of a histone deacetylase to target promoters could result in transcriptional repression and the generation of a repressive chromatin region. Using site-directed mutagenesis I also showed a direct correlation between histone deacetylase activity and transcriptional repression. Finally, as part of a collaborative

project, I demonstrated that a histone deacetylase could counteract genomic silencing. These studies had a significant impact on the field, since the mechanism of transcriptional repression by targeted histone deacetylation is evolutionarily conserved from yeast to mammals and known to play a role in a variety of disease processes.

- a. DeRubertis, F., **Kadosh, D.**, Henchoz, S., Pauli, D., Reuter, G., Struhl, K. and Spierer, P. (1996). The histone deacetylase Rpd3 counteracts genomic silencing in *Drosophila* and yeast. *Nature* 384: 589-591.
 - b. **Kadosh, D.** and Struhl K. (1997). Repression by Ume6 involves recruitment of a complex containing Sin3 corepressor and Rpd3 histone deacetylase to target promoters. *Cell* 89: 365-371. *Cover article, see commentaries: Pazin, M.J. and Kadonaga, J.T. Cell 89:325-328 (1997), Wolffe, A.P., Nature 387:16-17 (1997). Featured in Focus newsletter (Harvard Medical School, May 2, 1997)*
 - c. **Kadosh, D.** and Struhl K. (1998). Histone deacetylase activity of Rpd3 is important for transcriptional repression *in vivo*. *Genes Dev.* 12: 797-805.
 - d. **Kadosh, D.** and Struhl K. (1998). Targeted recruitment of the Sin3-Rpd3 histone deacetylase complex generates a highly localized domain of repressed chromatin *in vivo*. *Mol. Cell. Biol.* 18: 5121-5127.
2. My laboratory has made significant contributions towards our understanding of key mechanisms important for controlling *C. albicans* morphology and virulence. More specifically, we have shown that expression levels of a filament-specific transcriptional regulator, *UME6*, are sufficient to determine all three morphologies by a common dosage-dependent mechanism and promote virulence. These results challenged the previous paradigm that *C. albicans* pseudohyphal and hyphal morphologies are controlled by genetically distinct mechanisms. We have also demonstrated that Ume6 promotes hyphal growth and biofilm formation via a mechanism involving the Hgc1 cyclin-related protein. Finally, we have recently shown that a 5' UTR-mediated translational efficiency mechanism inhibits the *C. albicans* morphological transition and can be modulated by host environmental cues. This finding represented the first demonstration that a major virulence property of a human fungal pathogen is controlled at the translational level and is likely to have a significant impact on the field, given that many important regulators of *C. albicans* morphology, virulence and virulence-related processes also possess long 5' UTRs.
- a. Carlisle, P.L., Banerjee, M., Lazzell, A., Monteagudo, C., Lopez-Ribot, J.L. and **Kadosh, D.** (2009). Expression levels of a filament-specific transcriptional regulator are sufficient to determine *C. albicans* morphology and virulence. *Proc. Natl. Acad. Sci. USA* 106: 599-604. *Cover article, see Commentary: Bastidas, R.J. and Heitman, J., Proc. Natl. Acad. Sci. USA 106:351-352 (2009).*
 - b. Carlisle, P.L. and **Kadosh, D.** (2010). *Candida albicans* Ume6 a filament-specific transcriptional regulator, directs hyphal growth via a pathway involving Hgc1 cyclin-related protein. *Eukaryot. Cell* 9:1320-1328. PMID: PMC2937344
Featured as a Spotlight article, Eukaryot. Cell 9:1299 (2010).
Featured in the Journal Highlights section of ASM Microbe magazine, Microbe 5(10): 439 (2010).
Featured in HSC News, Volume XLII, Issue 21, October 19, 2010.
 - c. Banerjee, M., Uppuluri, P., Zhao, X.R., Carlisle, P.L., Vipulandandan, G., Villar, C.C., Lopez-Ribot, J.L. and **Kadosh, D.** (2013). Expression of *UME6*, a key regulator of *C. albicans* hyphal development, enhances biofilm formation via Hgc1- and Sun41-dependent mechanisms. *Eukaryot. Cell* 12(2):224-232. PMID: PMC3571304
 - d. Childers, D.S., Mundodi, V., Banerjee, M. and **Kadosh, D.** (2014). A 5' UTR-mediated translational efficiency mechanism inhibits the *Candida albicans* morphological transition. *Mol. Microbiol.* 92(3):570-585. PMID: PMC4032089
Faculty of 1000 "recommended".
3. The availability of the complete sequence and annotation for the *C. albicans* genome has greatly facilitated genome-wide transcriptional analyses. Taking advantage of this resource, I used DNA microarrays to define the complete set of *C. albicans* genes induced in response to strong filament-inducing conditions. Many genes involved in multiple biological processes were identified by this analysis (and other analyses), several of which (eg: *UME6* and *BCR1*) have been subsequently shown to play important roles in *C. albicans* morphology, virulence, biofilm formation and virulence-related processes. Using genome-wide transcriptional profiling and bioinformatics analysis our laboratory has

also defined genes and gene classes specifically associated with determination of *C. albicans* pseudohyphal and hyphal morphologies. We also demonstrated that genes associated with the pseudohyphal morphology are a subset of those associated with hyphal growth and are generally expressed at lower levels. In addition, we observed fundamental differences in the transcriptional profiles associated with forward and reverse *C. albicans* morphological transitions. These studies have had a significant impact on our understanding of genome-wide expression changes associated with morphological transitions in pathogenic fungi.

- a. **Kadosh, D.** and Johnson, A.D. (2005). Induction of the *Candida albicans* filamentous growth program by relief of transcriptional repression: a genome-wide analysis. *Mol. Biol. Cell* 16: 2903-2912. PMCID: PMC1142434
 - b. Carlisle, P.L. and **Kadosh, D.** (2013). A genome-wide transcriptional analysis of morphology determination in *Candida albicans*. *Mol. Biol. Cell* 24(3):246-260. PMCID: PMC3564527
 - c. Albataineh, M.T., Lazzell, A., Lopez-Ribot, J.L. and **Kadosh, D.** (2014). Ppg1, a PP2A-type protein phosphatase, controls filament extension and virulence in *Candida albicans*. *Eukaryot. Cell* 13(12):1538-1547 PMCID: PMC4248689
 - d. Childers, D.S. and **Kadosh, D.** (2015). Filament condition-specific response elements control the expression of *NRG1* and *UME6*, key transcriptional regulators of morphology and virulence in *Candida albicans*. *PLoS One* 10(3):e0122775 PMCID: PMC4374957
4. Considerably little is known about the evolution of regulatory mechanisms important for controlling morphology in pathogenic *Candida* species. We have defined specific optimal environmental conditions that induce filamentation in three non-*albicans* *Candida* species (NACS) which are already starting to pave the way for additional work in the field on NACS filamentation. We have also demonstrated that an evolutionary weakness in the induction of conserved orthologs of *C. albicans* filament-specific target genes can be partially overcome by high-level expression of *UME6* orthologs. *NRG1* also appeared to function as a repressor of filamentation in several, but not all, NACS. These findings are significant because they suggest that *C. albicans* morphological regulatory functions are partially conserved in NACS as well as a novel hypothesis that filamentation ability may have evolved with strength of filament-specific gene expression.
- a. Lackey, E., Vipulanandan, G., Childers, D.S. and **Kadosh, D.** (2013). Comparative evolution of morphological regulatory functions in *Candida* species. *Eukaryot. Cell* 12 (10):1356-1368. PMCID: PMC3811340
Featured as a Spotlight article, Eukaryot. Cell 12(10):1315 (2013).
 - b. **Kadosh, D.** Najvar, L.K., Bocanegra, R., Olivo, M., Kirkpatrick, W.R., Wiederhold, N.P., Patterson, T.F. (2016). Effect of antifungal treatment in a diet-based murine model of disseminated candidiasis acquired via the gastrointestinal tract. *Antimicrob. Agents Chemother.* 60(11):6703-6708. PMCID: PMC5075076

Complete List of Published Work:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/david.kadosh.1/bibliography/40629089/public/?sort=date&direction=descending>

D. Research support

CURRENT

NIH/NIAID

5R01AI083344 (PI: David Kadosh) \$261,211/yr. direct costs (5/15/10-4/30/17)
Determination of Morphology and Virulence in *Candida albicans*

NIH/NIAID

5R21AI117299 (PI: David Kadosh) Year 1: \$160,637, Year 2: \$135,637 direct costs (6/15/15-5/31/17)
Evolution of the Morphology-Virulence Relationship in *Candida* species

Note: an automatic no-cost extension is planned until 5/31/18.

NIH/NIAID

1R21AI129883 (PI: David Kadosh) Year 1: \$157,887, Year 2: \$125,000 directs costs (12/15/16-11/30/18)
Translational Control of *Candida albicans* Biofilm Development and Maintenance

Note: an automatic no-cost extension is planned until 11/30/19.

NIH/NIAID

1R21AI130668 (PI: David Kadosh) Year 1: \$132,887, Year 2: \$150,000 directs costs (1/5/17-12/31/18)
Translational Control of Antifungal Resistance in *Candida albicans*

Note: an automatic no-cost extension is planned until 12/31/19.

NIH/NIAID

HHSN272201000038I/HHSN27200005 NIH Contract (PI: Thomas Patterson) (3/1/16-10/31/17)

Task A93 – Therapeutics Testing in Murine Models of Fungal Infections – Aspergillosis, Candidiasis,
Mucormycosis

Base Award: \$822,261 Total contract with options: \$1,877,513

Role: Co-Investigator

PENDING

NIH/NIAID

1R01AI127692 (PI: David Kadosh) \$257,886/yr. direct costs (7/1/17-6/30/22)
Translational Control of Morphology and Virulence in *Candida albicans*

NIH/NIDCR

1R01DE027085 (PI: David Kadosh) \$261,750/yr. direct costs (7/1/17-6/30/22)
Dynamics and Antifungal Resistance of Mixed *Candida* Species Biofilms in the Oral Cavity

NIH/NIDCR

2R01DE021084 (PI: Chih-Ko Yeh) \$308,300/yr. direct costs (7/1/17-6/30/22)
Rechargeable Long-term Anticandidal Denture Materials
Role: Collaborator

COMPLETED (last 3 years)

American Heart Association Southwest Affiliate

16GRNT30670002 (PI: David Kadosh) \$70,000/yr. direct costs (7/1/16-12/14/16)
Identification and Characterization of Factors with Novel Roles in *Candida albicans* Biofilm Development

Voelcker Fund Young Investigator Award (PI: David Kadosh) \$136,364/yr. direct costs (7/01/09-6/30/16)
Identification of New Antifungal Targets to Treat Cancer and Heart Patients

Institute for Integration of Medicine and Science-Clinical and \$50,000 direct costs (10/1/14-9/30/15)
Translational Science Award (IIMS/CTSA) (PI: David Kadosh)
Development of a Novel Antifungal Treatment for *Candida* Species Biofilms

SALSI Innovation Challenge Award (Co-PI: David Kadosh) \$100,000 direct costs (9/1/14-6/14/15)
San Antonio Life Sciences Institute (SALSI)
Challenging the Morphology-Virulence Paradigm in Pathogenic *Candida* Species

NIH/NIAID

HHSN272201000038I/HHSN27200001 NIH Contract (PI: Thomas Patterson) (9/13/10-3/12/15)

Task A13 - Small Animal Model Development and Utilization for Target Identification and Testing of
Diagnostics, Therapeutics and Vaccines for Selected Invasive Fungal Diseases.

Base Award: \$816,969 (9/13/10 – 9/12/12) – total contract with options: \$8,262,013

Role: Co-Investigator

Kadosh Lab Xiangya Student Research Projects

Our laboratory's research is focused on molecular mechanisms that control fungal pathogenesis with a specific emphasis on *Candida* species. Normally found as commensals in the mammalian host, *Candida* species are capable of causing mucosal infections, such as oral and vaginal thrush, as well as a variety of more serious systemic infections. Approximately 70% of all women will experience at least one episode of vaginal candidiasis during their lifetime. Candidiasis is also the fourth-leading cause of hospital-acquired bloodstream infections in the U.S., with a mortality rate approaching 35-60%. A wide variety of immunocompromised individuals are particularly susceptible, including AIDS patients, organ transplant recipients, neonates, cancer patients undergoing chemotherapy and recipients of artificial joints and prosthetic devices. Approximately \$1 billion is spent per year on the treatment of patients with hospital-acquired *Candida* infections in the U.S. alone. However, only three major classes of antifungals are available and there is a significant demand to develop new and more effective antifungal therapies.

Translational Control of Morphogenesis, Biofilm Formation and Antifungal Resistance in the Major Human Fungal Pathogen *Candida albicans*. Approximately 50% of *Candida* infections can be attributed to *Candida albicans*, the major human fungal pathogen. *C. albicans* possesses a number of important virulence properties, including the ability to adhere to host cells, secrete degradative enzymes, form biofilms (highly drug-resistant surface-attached microbial communities encased in an extracellular matrix) and undergo a reversible morphological transition from single-celled yeast to filaments (elongated cells attached end-to-end) that can invade tissues and lyse macrophages. Resistance to the limited arsenal of antifungal drugs also continues to represent an important problem with clinical consequences. While many previous studies from our laboratory and other laboratories have examined transcriptional mechanisms that regulate these virulence properties, very little is known about translational mechanisms that control the pathogenicity of *C. albicans* or other human fungal pathogens. However, we have recently demonstrated that a major transcriptional regulator of *C. albicans* morphogenesis, biofilm formation and virulence is controlled by a 5' UTR-mediated translational efficiency mechanism in response to host environmental cues (Childers, *et al.*, *Mol. Microbiol.* 92(3):570-585). We are currently using a recently developed and very powerful deep sequencing approach, ribosome profiling, to specifically define translational gene expression changes associated with *C. albicans* morphogenesis, biofilm formation and antifungal resistance. In addition to providing one of the first pictures of the *C. albicans* global translational landscape, these experiments will also identify a variety of new factors associated with key *C. albicans* virulence properties that are likely to serve as potential targets for the development of novel antifungal therapies. Xiangya students will be involved in characterizing the role of one or several of these factors in controlling multiple *C. albicans* virulence traits including morphogenesis, biofilm formation, antifungal drug resistance, secreted degradative enzyme production and/or adhesion. Many opportunities will be available to gain experience in a variety of laboratory techniques in molecular biology, genetics, genomics, biochemistry, cell biology and microscopy.

Evolution of Morphology and Virulence in *Candida* species. The remaining 50% of *Candida* infections that are not caused by *C. albicans* can be attributed to several less pathogenic non-*albicans* *Candida* species (NACS). These species are thought to be less pathogenic than *C. albicans* because they do not filament as readily or adhere as tightly to host cells, although several of these species are intrinsically more resistant to antifungal drugs. The recent publication of genome sequences for NACS has facilitated studies in our lab that seek to determine how and why *C. albicans* evolved to become the most pathogenic *Candida* species. We have defined specific filament-inducing conditions for two NACS, *Candida tropicalis* and *Candida parapsilosis*, and demonstrated that several key transcriptional mechanisms important for controlling *C. albicans* morphogenesis and biofilm formation are conserved over evolution in NACS (Lackey, *et al.*, *Eukaryot. Cell* 12(10):1356-1368). Xiangya students will be involved in determining the extent to which a wider variety pathogenesis mechanisms are evolutionarily conserved across *Candida* species. Ultimately, information gained from these studies should aid in designing more effective broad-spectrum antifungal therapies that target conserved virulence mechanisms in a variety of pathogenic *Candida* species.

For additional information regarding our laboratory research please see our website: <http://uthscsa.edu/mimg/faculty/dk/dk.asp>